Please replace the first paragraph on page 12 with the following rewritten paragraph:

-- Referring to FIG. 3, uniformly distributed random conformations are generated allowing only rotatable bonds to vary 310. For example, 1,000 uniformly distributed random conformations can be generated varying only the rotatable bonds. The internal energy of each conformation is then minimized, again allowing only rotatable bonds to vary 320. Internal energy can be estimated, for example, using van der Waals potentials and dihedral angle term, reference: Diller, D.J. and C.L.M.J. Verlinde "A Critical Evaluation of Several Global Optimization Algorithms for the Purpose of Molecular Docking," Journal of Computational Chemistry, 1999, Vol. 20(16), p. 1740-1751, which is hereby incorporated herein by reference in its entirety. Each conformation can be minimized using, for example, a BFGS (Broyden-Fletcher-Goldfarb-Shanno) optimization algorithm. The algorithm is an updating formula used to iteratively build up an approximation of the minimum of a function *f*. The formula has the form:

$$x_{i+1} = x_i - H_i \bullet \nabla f_i$$

$$H_{i+1} = H_i + \frac{\left(x_{i+1} - x_i\right) \otimes \left(x_{i+1} - x_i\right)}{\left(x_{i+1} - x_i\right) \cdot \left(\nabla f_{i+1} - \nabla f_i\right)} - \frac{\left[H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)\right] \otimes \left[H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)\right]}{\left(\nabla f_{i+1} - \nabla f_i\right) \cdot H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)} +$$

$$\left[\left(\nabla f_{i+1} - \nabla f_i\right) \cdot H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)\right] u \otimes u$$

where u is defined as the vector

$$u \equiv \frac{\left(x_{i+1} - x_i\right)}{\left(x_{i+1} - x_i\right) \cdot \left(\nabla f_{i+1} - \nabla f_i\right)} - \frac{H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)}{\left(\nabla f_{i+1} - \nabla f_i\right) \cdot H_i \cdot \left(\nabla f_{i+1} - \nabla f_i\right)}$$

where

x_i is the vector of the initial position of the ligand;

x_i is the vector of the initial position of the ligand;

x_{i+1} is the updated vector of the position of the ligand;

f_i is the function to be minimized, in this case, internal energy;

∇f_i is the gradient, or second derivative, of the function;

∇f_{i+1} is the updated gradient of the function;

H_i is the ith approximation to the inverse of the Hessian matrix (second derivatives of f);

and

H_{i+1} is the updated approximation to the inverse of the Hessian matrix. --

Please replace the last paragraph on page 17, through line 3 on page 18:

-- Each remaining match is optimized using BFGS optimization algorithm as described above, wherein a simple atom pairwise score is the function which is minimized 640. In one embodiment, the score can be modeled after the Piecewise Linear Potential (see, Gehlhaar, D.K., et al., "Molecular Recognition of The Inhibitor AG-1343 By HIV-1 Protease: Conformationally Flexible Docking by Evolutionary Programming," Chemistry & Biology, 1995, Vol. 2, p. 317-324, which is hereby incorporated herein by reference in its entirety) with a difference being that the score used herein is preferably differentiable. For this score, all hydrogens are ignored, and all non-hydrogen atoms are classified into one of four categories:

In the Claims:

Please amend claims 1, 4, 6, 8-11, 14, 16, 18-21, 24, 26 and 28-30 as follows:

(Amended) 1. A method of docking a ligand to a protein comprising:

performing a pre-docking conformational search to generate multiple solution conformations of the ligand;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the ligand to obtain at least one ligand position relative to the protein in a ligand-protein complex formation; and